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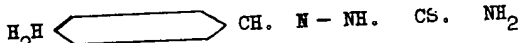
## TREATMENT OF TUBERCULOSIS WITH THIOSEMICARBAZONE

(From a paper read in Warsaw on 26 May 1950 at a meeting of the Science Committee of Chemotherapy in Tuberculosis by Dr Kazimierz Dabrowski, director of the State Sanatoria in Zakopane)

TbI, 4-acetylaminobenzaldehyde-thiosemicarbazone (called "conteben" in Western Germany, "tebetion" in Eastern Germany, "tibition" by Schenley Laboratories, "myrizon" by E. R. Squibb and Sons, "panron" by the Panray Corporation) was synthesized in the US by three chemists, Behnisch, Mietzsch, and Schmidt. In Poland, the synthesis was accomplished by J. Supniewski and the products is being put out by "Neutron" in Myslowice under the name of ATB.

The thiosemicarbazone of aminobenzaldehyde appears to be the simplest thiosemicarbazone:



This is not a very effective compound but is a very important intermediate for other compounds. A very effective TbI is produced by introducing an acetyl group. By changing the left side of the formula, other valuable compounds may be obtained. If, for instance, an alkyl grouping contains an alkaline or acid group, a compound soluble in water results. The German product TbVI is a compound soluble in water which has a somewhat weaker effect than TbI. Supniewski also synthesized a soluble thiosemicarbazone, but its toxicity remains to be tested.

Pharmacological research by J. Supniewski at the Pharmacological Institute of the Krakow Academy of Medicine proved that animals could tolerate a dose of 40 milligrams of thiosemicarbazone per kilogram without ill effect. A doze of 60 milligrams per kilogram resulted in death. The animals did not die suddenly, so that cumulative action of the drug must be assumed.



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Histopathological post-mortem tests showed extensive damage to the liver, kidneys, and adrenal glands. Tests of extravasations showed that thiosemicarbazone is harmful to the capillaries. Blood corpuscles increased in size, the globulin content diminished, and the albumin content increased. The sugar content of the blood was reduced. In 24-48 hours after administering the drug, assimilation of gas was reduced, and the respiratory coefficient diminished. Thiosemicarbazone apparently blocks oxidation within the cells.

This appears to be the only research of its kind relating to thiosemicarbazone since there is no mention of it in German, French, and American publications available to the author.

To apply thiosemicarbazone locally, a suspension of pure powder in a physiological salt solution is prepared. To 5 grams of powder up to 50 milliliters of the salt solution are added. The suspension is Tyndallized by heating in a rubber-stoppered vial 30 minutes a day for 3 successive days at 65 degrees centigrade. The sterilized suspension is stored in a dark, cool place. The suspension must be well shaken and mixed before using and its sterility must be maintained. One milliliter of this 10-percent suspension contains 100 milligrams of powder.

Konteben is on sale in jars of 5 grams of pure substance and in tablets of .025 and 0.05 gram. At present in Poland, ATB tablets of 100 milligrams are available.

In the early stage of experiments with thiosemicarbazone, TbI/698E was used, containing 0.125 gram each of the thiosemicarbazone and eleudron. This proved very toxic and was withdrawn.

It is not yet known how fast the product is resorbed, what concentration is reached in the tissues and blood, how fast it is eliminated, or how fast catabolism takes place. Tests on concentration in body fluids are very difficult and are possible only in very well-equipped chemical laboratories. The usual doses result in concentration in the blood which is harmful to tuberculosis bacilli. A culture of tuberculosis bacilli prepared with serum from patients treated with thiosemicarbazone showed that the bacilli changed form and color and even disintegrated.

It was determined that a daily dosage of 100 milligrams is eliminated by the system in 24 hours.

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